Pergamon

Tetrahedron, Vol. 52, No. 18, pp. 6361-6372, 1996

0040-4020/96 $15.00 + 0.00

S0040-4020(96)00295-5

Total Synthesis of (±)-Halipanicine

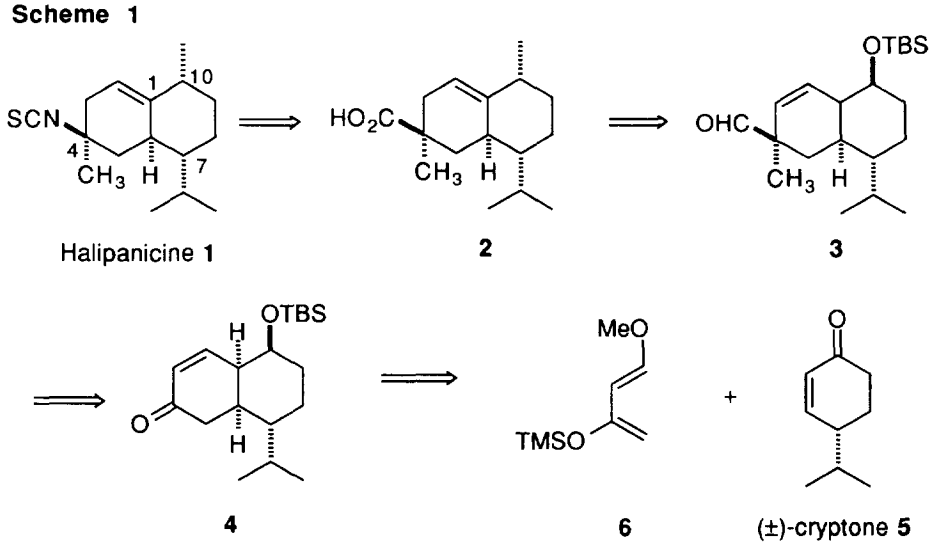
Bin Ye, Hideshi Nakamura*, and Akio Murai

Division of Chemistry, Graduate School of Science, Hokkaido University, Sapporo 060, Japan

Abstract: A total synthesis of (±)-halipanicine is described. A Diels-Alder reaction and Martin's methodology were successfully utilized at the key steps to construct the AB-ring and to secure stereochemistry at the C-4 position, respectively. The relative stereochemistry of halipanicine was established by a sequence of stereospecific reactions.

In recent years, a number of natural products bearing an isothiocyanate group have been isolated from marine organisms and plants, as well as microorganisms.[1] These possess various biological activities and act as opioid antagonists, antifeedants, and anticarcinogenic agents.[1,2] For this reason, extensive studies have been conducted in areas related to their synthesis, structure and activity relationships, and biology.[2,3] In 1986, during our studies on bioactive marine natural products, halipanicine **1**,[4] a novel sesquiterpene was isolated from the Okinawan marine sponge *Halichondria panicea*. It differs from known sesquiterpene isothiocyanates,[1] and has a unique structure characterized by the location of the isothiocyanate group on a C-4 quaternary carbon, as well as having a cis orientation of the methyl group at C-10 relating to isopropyl group at C-7. Its limited availability from natural sources has restricted its further biological evaluation, and its absolute stereochemistry remains unclear. Therefore, we initiated a program to complete its total synthesis in order to provide sufficient material for biological testing and to solve its absolute stereochemistry. We recently reported the racemic synthesis,[5] and herein, we describe our detailed results.

Scheme 1

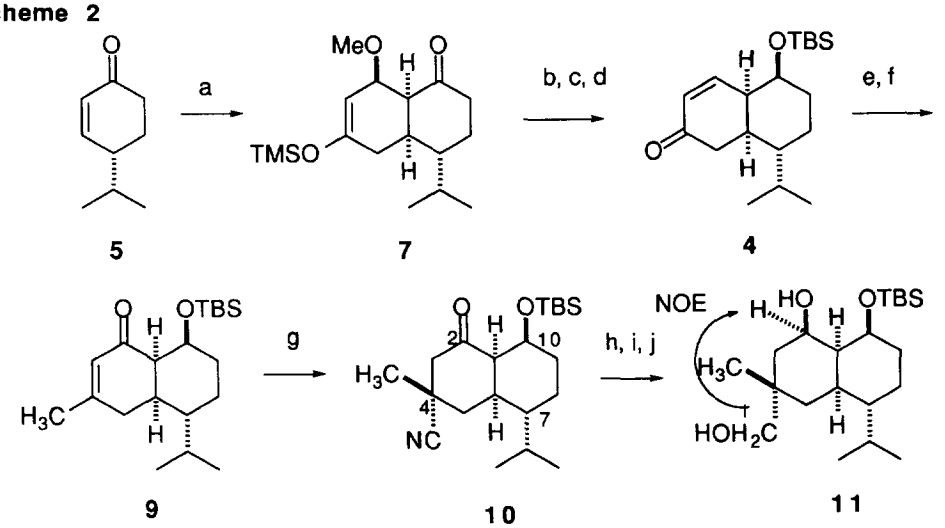


Results and Discussion

Our retrosynthetic analysis for the synthesis of halipanicine **1** is outlined in Scheme 1, in which two axial methyl groups at C-4 and C-10 should be introduced by stereospecific manner. We chose to introduce the unstable isothiocyanate group at the end of the synthesis utilizing Curtius reaction[6] and further conversions of olefin-acid **2**. The compound **2**, in turn, should be available from olefin-aldehyde **3** by a sequence of transformations including stereoselective introduction of a methyl group at the C-10 position and olefin formation at the C-1 position. The key intermediate **3** can be derived through stereoselective introduction of the methyl and aldehyde groups onto α,ß-unsaturated ketone **4**. Finally, the cadinane backbone of **4** was built *via* the Diels-Alder reaction of Danishefsky diene **6**[7] with (±)-cryptone **5**.[8]

Initially, we attempted to follow Burk's route[9] to build cadinane skeleton through the Diels-Alder reaction of (±)-cryptone **5** with 2-ethoxy-1,3-butadiene. Both of these starting material were prepared according to known procedures.[8,10] However, the reaction failed under either thermal or Lewis acid catalyzed conditions. A much more active diene, the Danishefsky diene **6**, was then employed. Its reaction with (±)-cryptone in a 4 to 1 ratio proceeded smoothly in a sealed tube at 180-185 °C for 22 h to yield crude adduct **7** and α, ß-unsaturated ketone **4** was obtained by reduction with diisobutylaluminum hydride (Dibal-H), successive hydrolysis and protection with TBSCl in 50% overall yield from (±)-cryptone **5** (Scheme 2). The relative configuration of α,ß-unsaturated ketone **4** was established through ^{1}H NMR decoupling experiments.

Scheme 2

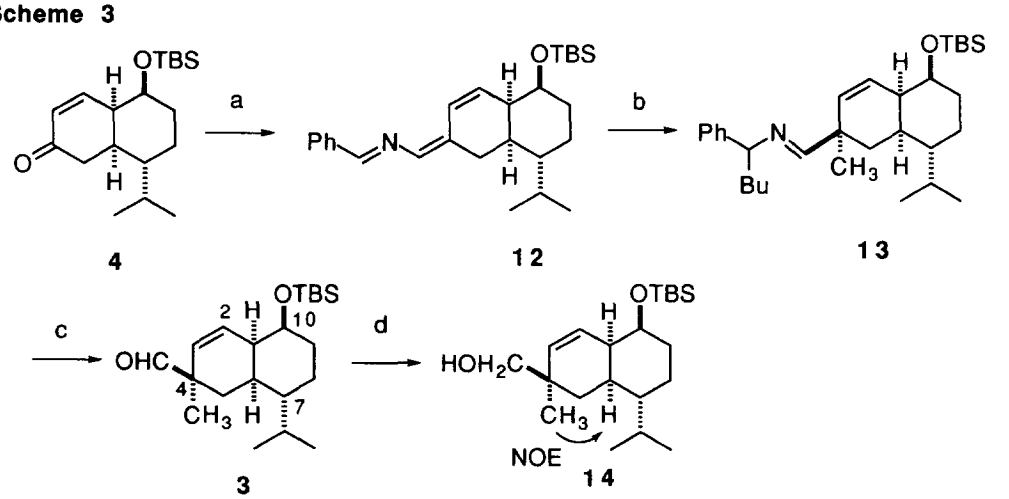


Reagents and conditions: a) **6** (4 eq.), 0.5% mol 2,6-di-*t*-butyl-*p*-cresol, 180-185 °C, 22 h. b) Dibal-H, CH_2Cl_2, -78 °C, 1h. c) 0.5 M HCl-THF (4:15), 20 °C, 12 h. d) TBSCl, imidazole, DMF, 20 °C, 3 h, 50% from **5**. e) MeMgI, ether, rt, 4 h, 97%. f) PDC, CH_2Cl_2, rt, 12 h, 98%. g) TMSCN, Et_3Al, CH_2Cl_2, rt, 4 h, 63%. h) $NaBH_4$, MeOH, 0 °C, 30 min, 88%. i) Dibal-H, toluene, -78 °C, 30 min, 79%. j) $NaBH_4$, MeOH, 0 °C, 30 min, 97%.

With the key intermediate **4** in hand, we first tried to introduce methyl and oxidized methyl functionalities onto C-4 position. Transformation of the α,ß-unsaturated ketone **4** to **9** is depicted in Scheme 2. Treatment of **4** with Grignard reagent MeMgI in ether at rt for 3 h gave allylic alcohol **8** in 97% yield, which was oxidized with PDC in dichloromethane at rt for 12 h to afford **9** in 98% yield. Subsequent Michael addition of TMSCN to α,ß-unsaturated ketone **9** in the presence of Et_3Al at rt for 4 h gave a nitrile **10** in 63% yield. Unfortunately, the stereochemistry of the methyl group at the C-4 position deduced by NOE experiments on the reduced compound **11** was opposite to that desired. A nitrile with the desired stereochemistry could not be obtained under various kinetic or thermodynamic conditions.

Therefore, we turned our attention to the Martin's one pot methodology,[11] in which a ketone carbonyl group can be easily converted into a quaternary carbon having dissimilarly functionlized alkyl substituents. This approach allows inverted introduction of the two functional groups onto ketone **4** to secure the correct C-4 stereochemistry (Scheme 3). Treatment of **4** with a lithium salt of diethyl benzylideneaminomethylphosphonate Ph-CH=N-C(Li)H-P(=O)$(OEt)_2$, generated from metalation of N-benzylideneaminomethylphosphate prepared according to the literature method,[5,13] gave the corresponding 2-azadiene **12**. Regiospecific addition of butyllithium to the 2-azadiene **12** produced the metalloenemine, Ph-C(Bu)H-NLi-CH=CRR'. Methylation of the metalloenamine with iodomethane proceeded stereospecifically from the convex side to give intermediate **13**, which was hydrolyzed to afford aldehyde **3** as a single isomer in 87% total yield from α,ß-unsaturated ketone **4**. The aldehyde **3** was reduced with $NaBH_4$ to yield the corresponding alcohol **14** in 91% yield. The configuration of the newly formed quaternary carbon was established based on the NOE increment of the H-6 proton by irradiation at the tertiary methyl group.

Scheme 3

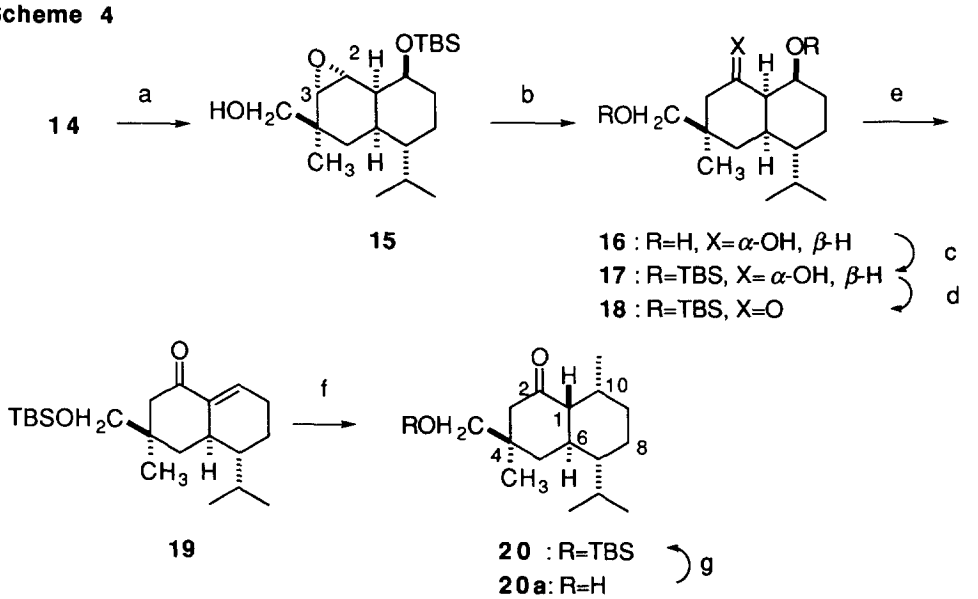


4 **12** **13** **3** **14**

Reagents and conditions: a) Ph-C=N-C⁻H-P(=O)$(OEt)_2Li^+$, THF, -78-25 °C, 2 h. b) BuLi, -78 ° C, 1 h, then MeI, -78-20 °C, 2 h; c) 1 M HCl, 20 °C, 2 h, 87%. d) $NaBH_4$, MeOH, 0 °C, 30 min, 91%.

The introduction of the methyl group at the C-10 position was achieved by cuprate addition to enone **19**, which was derived from **14** by the following 5 steps (Scheme 4). Oxidation of alcohol **14** with *m*-chloroperbenzoic acid afforded epoxide **15** in a quantitative yield. Conditions were then examined for regioselective reduction of the epoxide at the C-3 position. Finally, $LiAlH_4$ in dioxane gave the best result of triol **16** formation in 75% yield, accompanied by 22% of C-2 reduced products among the conditions such as $LiAlH_4$ in THF (C-3 reduction 55% and C-2 reduction 30%), $LiAlH_4$ in diglyme (C-3 38% and C-2 29%), Li-ethylenediamine in THF (C-3 28% and C-2 45%) and Red-Al in THF (no reaction). Selective protection of diol **16** with TBSOTf at -20 °C formed bis-TBS ether **17** in 87% yield, which upon oxidation with PDC gave ketone **18** in 99% yield. ß-Elimination of ketone **18** using 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU) in refluxing xylene for 5 h afforded α,ß-unsaturated ketone **19** in 95% yield. Stereoselective introduction of a methyl group at the C-10 position was achieved as expected upon treatment of **19** with Me_2CuLi in the presence of $BF_3{\cdot}OEt_2$ to give the desired product **20** in 76% yield, accompanied by deprotected product **20a** in 15% yield. The latter could be converted into **20** in 98% yield by treatment with TBSOTf. The relative stereochemistry of **20** was determined from the decoupling ($J_{H1\text{-}H6}=J_{H6\text{-}H7}$= 11 Hz, $J_{H1\text{-}H10}\cong 0$ Hz) and NOE experiments (C10Me to H6).

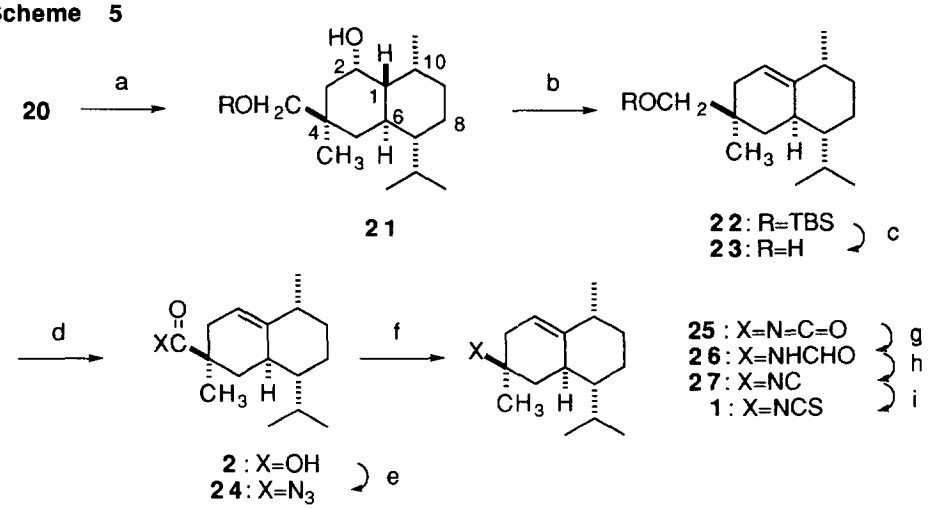
Scheme 4



Reagents and conditions: a) *m*-CPBA, CH_2Cl_2, 20 °C, 5 h, 100%. b) $LiAlH_4$, dioxane, 80-85 °C, 1.5 h, 75%. c) TBSOTf, Et_3N, DMAP, CH_2Cl_2, -20 °C, 30 min, 87%. d) PDC, MS4A, CH_2Cl_2, 20 °C, 5 h, 99%. e) DBU, xylene, reflux, 5 h, 95%. f) $Me_2CuLi{\cdot}$ LiI, $BF_3{\cdot}OEt_2$, THF, -78 °C, 76%. g) TBSOTf, Et_3N, DMAP, CH_2Cl_2, -20 °C, 30 min, 98%.

Transformation of ketone **20** into the final product is described in Scheme 5. Reduction of ketone **20** with $NaBH_4$ gave a single isomer **21** with an axial hydroxyl group in 86%, which was quantitatively converted into olefin **22** by the treatment with thionyl chloride in pyridine at 0 °C. Removal of TBS protection of olefin **22** with TBAF followed by oxidation with Jones' reagent afforded olefin-acid **2** in 94% overall yield. A modified Curtius reaction[16] was utilized to convert **2** into isocyanate **25** with retention of the stereochemistry. Treatment of olefin-acid **2** with 1 eq of KH and diphenylphosphoryl azide (DPPA) at 0 °C in THF for 2.5 h, then reflux in xylene for 5 h afforded olefin-isocyanate **25** in 98% yield. Reduction of olefin-isocyanate **25** with lithium triethylborohydride in THF at -78 °C followed by treatment with *p*-toluenesulfonyl chloride and pyridine provided olefin-isonitrile **27** in 83% overall yield. Finally, heating **27** with sulfur in xylene at 120-125 °C for 4 h afforded (±)-halipanicine **1** in 63% yield. The synthetic halipanicine was spectrally identical with natural product.

Scheme 5



Reagents and conditions: a) $NaBH_4$, MeOH, 20 °C, 86% . b) $SOCl_2$, Py, 0 °C, 1 h, 100%. c) TBAF, THF, 40 °C, 12 h, 100%. d) Jones oxidation, 0 °C, 50 min, 94%. e) KH, $(PhO)_2P(=O)N_3$, THF, 0-20 °C, 3 h. f) xylene, reflux, 5 h, 98% from**2**. g) $LiEt_3BH$, THF, -78 °C, 1 h, 96%. h) TsCl, Py, 20 °C, 15 h, 87%. i) S_8, xylene, 120-125 °C, 4 h, 63%.

In conclusion, the total synthesis of (±)-halipanicine has been completed for the first time in 21 steps in 7.7% overall yield from (±)-cryptone. A series of the stereospecific reactions confirmed the relative stereochemistry of halipanicine. The synthesis successfully employed Diels-Alder reaction to construct the AB-ring, and exploited Martin's methodology to secure the stereochemistry at the C-4 position. Further studies toward the enantiospecific synthesis of halipanicine are in progress.

Experimental Section

General. Solvents were dried and distilled before use. Ether, tetrahydrofuran (THF), and toluene were distilled from sodium benzophenone ketyl. Dichloromethane and pyridine were distilled from calcium hydride. Molecular sieves 4 Å (MS4A) was finely powered and activated at 180 °C for 5 h *in vacuo*. Reagent-grade solvents were used for chromatography and extraction. All reactions were monitored by thin-layer chromatography with precoated silica gel plates (E. Merck, Silica gel 60 F_{254} Art.5554). Flash chromatography utilized silica gel (E. Merck, Silica gel 60, 70-230 mesh, Art. 7734). Infrared (IR) spectra were obtained on a Hitachi model 270-30 infrared spectrophotometer. ^{1}H NMR spectra were recorded on a JEOL model GX-400 (400 MHz) spectrometer in $CDCl_3$ unless stated otherwise. Splitting patterns are designated as "s, d, t, q, m, and br"; indicating "singlet, doublet, triplet, quartet, multiplet, and broad", respectively. Low-and high-resolution mass spectra (LR-MS and HR-MS) were obtained on a JEOL model JMS-DX-300 or JMS-HX-110 mass spectrometers. All reactions were carried out under anhydrous conditions and in an argon atmosphere, unless otherwise noted.

(4aα,5β,8α,8aα)-5-[(tert-Butyldimethylsilyl)oxy]-4a,5,6,7,8,8a-hexahydro-8-(1-methylethyl)-2(1H)-naphthalenone 4: A mixture of (±)-cryptone **5** (1.71 g, 12.4 mmol), Danishefsky diene **6** (8.52 g, 49.5 mmol) and 2, 6-di-*t*-butyl-*p*-cresol (12.0 mg) was placed in a glass tube, cooled to -78 °C, and oxygen removed under vacuum and recharged with argon three times, then sealed and kept at 180-185 °C for 22 h. After cooling to rt, the sealed tube was opened and the crude adduct **7** was diluted with dichloromethane (50 mL), then transferred to a dried flask. The crude product was reduced with Daibal-H (20 mL, 0.93 M in toluene, 18.6 mmol) at -78 °C under argon for 1 h. It was then quenched with acetone (10 mL), diluted with ether (150 mL), washed with 10% NaOH (3x30 mL), brine (2x50 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The resulting residue was dissolved in THF (30 mL) at rt, and 0.5 M HCl (8 mL) was added, then stirred at rt overnight. The mixture was extracted with ether (3x50 mL), washed with 5% $NaHCO_3$ (20 mL), brine (2x15 mL), dried over Na_2SO_4, and concentrated *in vacuo*. Flash chromatography of the resulting residue (silica gel, 20% ethyl acetate in hexane) gave relatively pure α,ß-unsaturated ketone alcohol (2.12 g), which was protected with TBSCl (3.07 g, 20.3 mmol) and imidazole (1.53 g, 22.3 mmol) in DMF at rt under argon for 3 h. The reaction mixture was quenched with water (10 mL), extracted with ether (3x40 mL), washed with brine (2x10 mL), dried over Na_2SO_4, and concentrated *in vacuo*. Flash chromatography of the residue (silica gel, 3% ethyl acetate in hexane) gave α,ß-unsaturated ketone **4** as a colorless oil (2.0 g, 50%). **4**: IR (neat) 2960, 2930, 2900, 2860, 1690, and 890 cm^{-1}; ^{1}H NMR δ 7.16 (1H, dt, *J*=10, 2 Hz, H-2), 6.07 (1H, dd, *J*=10, 3 Hz, H-3), 3.77 (1H, dt, *J*=11, 5 Hz, H-10), 2.85 (1H, br m, H-1), 2.73 (1H, dd, *J*=16, and 2 Hz, H-3), 2.38 (1H, dd, *J*=16, 4 Hz, H-5α), 2.13 (1H, m, H-5ß), 1.88 (1H, m, isopropyl), 1.73 (1H, m, H-9α), 1.63 (1H, dq, *J*=13, 3 Hz, H-8ß), 1.40-1.22 (3H, m, H-7, H-8 , H-9ß), 0.90 (9H, s), 0.86 (3H, d, *J*=7 Hz), 0.72 (3H, d, *J*=7 Hz), 0.08 (3H, s), and 0.07 (3H, s); LR-EI-MS *m/z* 323 $(M+H)^+$, 307, 265, and 181; HR-EI-MS, calcd for $C_{19}H_{35}O_2Si$ $(M+H)^+$ 323.2406, found, 323.2390.

(2β,4aα,5β,8α,8aα)-5-[(tert-Butyldimethylsilyl)oxy]-1,2,4a,5,6,7,8,8a-octahydro-2-methyl-8-(1-methylethyl)-2-naphthol 8: Iodomethane (1.37 g, 9.57 mmol) was added to magnesium pieces (139 mg, 5.8 mmol) in ether (15 mL) at rt under argon, and the mixture was stirred until all magnesium had dissolved. A solution of **4** (621 mg, 1.93 mmol) in THF (10 mL) was then added at rt, and stirred for 3 h. The reaction mixture was diluted with ether (100 mL), washed with saturated solution of ammonium chloride (2x30 mL) and brine (10 mL), dried over Na_2SO_4, and concentrated *in vacuo*. Flash chromatography (silica gel, 5% ethyl acetate in hexane) gave olefin-alcohol **8** as a colorless oil (633 mg, 97%). **8**: IR (neat) 3540, 2987, 1637,1542, 937 cm^{-1}; ^{1}H NMR δ 5.94 (1H, dd, *J*=10, 2 Hz), 5.66 (1H, dd, *J*=10, 2 Hz), 3.70 (1H, dt, *J*=11, 5 Hz), 2.35 (1H, br), 2.24 (1H, dd, *J*=15, 3 Hz), 2.12 (1H, m), 2.00 (1H, m), 1.79-1.31 (6H, m), 1.28 (1H, m), 1.26 (3H, s), 0.89 (9H, s), 0.87 (3H, d, *J*=7 Hz), 0.73 (3H, d, *J*=7 Hz), 0.03 (3H, s), 0.01 (3H, s); LR-EI-MS *m/z* 338 (M^+), 320, 281, 191.

(4aα,5α,8β,8aα)-8-[(tert-Butyldimethylsilyl)oxy]-4,4a,5,6,7,8-hexahydro-3-methyl-5-(1-methylethyl)-1(8aH)-naphthalenone 9: Olefin-alcohol **8** (640 mg, 1.9 mmol) in dichloromethane (5 mL) was added to a mixture of PDC (1.41 g, 3.78 mmol) and MS4A (100 mg) in dichloromethane (15 mL) at rt. The mixture was stirred for 12 h, then poured into ether (40 mL) and filtered. The filtrate and combined ether washings were concentrated *in vacuo* and purified by flash chromatography (silica gel, 5% ethyl acetate in hexane) to give α,ß-unsaturated ketone **9** as a colorless oil (624 mg, 98%). **9**: IR (neat) 2986, 1697, 1653, 1240, 910 cm^{-1}; ^{1}H NMR δ 5.89 (1H, br. s, H-3), 4.22 (1H, br s, H-10), 2.90 (1H, dd, *J*=17, 12 Hz, H-5ß),

2.37 (1H, dt, *J*=12, 5 Hz, H-6), 2.25 (1H, dd, *J*=6, 3 Hz, H-1), 1.97 (1H, tt, *J*=14, 5 Hz, H-8β), 1.94 (3H, s, 4-CH_3), 1.92 (1H, dd, *J*=17, 5 Hz, H-5α), 1.68 (1H, m), 1.62-1.45 (2H, m), 1.08 (1H, br d, *J*=12 Hz), 0.94 (1H, m), 0.92 (3H, d, *J*=6 Hz), 0.89 (3H, d, *J*=6 Hz), 0.80 (9H, s), 0.07 (3H, s), 0.06 (3H, s); LR-EI-MS *m/z* 337 $(M+H)^+$, 321, 293, 279, 189; HR-EI-MS, calcd for $C_{20}H_{36}O_2Si$ (M^+) 336.2484, found 336.2462.

(3α,4aα,5α,8β,8aα)-8-[(tert-Butyldimethylsilyl)oxy]octahydro-3-cyano-3-methyl-5-(1-methylethyl)-1(2H)-naphthalenone 10: To a stirred mixture of **9** (167 mg, 0.50 mmol) and trimethylsilyl cyanide (109 mg, 1.1 mmol) in dichloromethane (10 mL) was added triethylaluminum (1.09 mL, 0.92 M in hexane, 10 mmol) in dichloromethane (10 mL) at rt. The reaction mixture was stirred for 4 h, then quenched with 10% NaOH (4 mL), extracted with ether (3x30 mL), washed with brine (10 mL), dried over Na_2SO_4, and concentrated *in vacuo*. To the resulting residue in THF (5 mL) was added 2 M HCl (1.5 mL) at 0 °C, and the mixture was stirred for 1 h, then extracted with ether (3x20 mL), washed with brine (5 mL) dried over Na_2SO_4, and concentrated *in vacuo*. Flash chromatography of the residue (silica gel, 10% ethyl acetate in hexane) gave cyano ketone **9** as a colorless crystal (115 mg, 63%) and recovered starting material (19.4 mg). **10**: mp 53-54 °C; IR ($CHCl_3$) 2932, 2864, 2236, 1713, 1467, and 1065 cm^{-1}; ^1H NMR δ 4.10 (1H, br s), 2.72 (1H, br d, *J*=16 Hz), 2.60-2.41 (2H, m), 2.45 (1H, dd, *J*=16, 5 Hz), 1.87 (1H, m), 1.71 (1H, br d, *J*=14 Hz), 1.63-1.50 (3H, m), 1.46 (3H, s), 1.32-1.20 (1H, m), 1.18 (1H, m), 0.96 (3H, d, *J*=7 Hz), 0.89 (3H, d, *J*=7 Hz), 0.88 (9H, s), 0.03 (3H, s), -0.06 (3H, s); LR-EI-MS *m/z* 364 $(M+H)^+$, 348, 306, 145; HR-EI-MS, calcd for $C_{21}H_{38}O_2NSi$ $(M+H)^+$ 364.2671, found 364.2701.

(1β,3α,4aα,5α,8β,8aα)-8-[(tert-Butyldimethylsilyl)oxy]decahydro-3-hydroxymethyl-3-methyl-5-(1-methylethyl)-1-naphthol 11: Sodium borohydride (18 mg, 0.47 mmol) was added to a stirred solution of **10** (115 mg, 0.32 mmol) in methanol (3 mL). The mixture was stirred at 0 °C for 30 min, then quenched with 10% HCl (4 mL), extracted with ether (3x20 mL), washed with brine (5 mL), dried over Na_2SO_4, and concentrated *in vacuo*. Flash chromatography of the residue (silica gel, 15% ethyl acetate in hexane) gave a cyano-alcohol (101 mg, 88%). A portion was subjected to reduction with Dibal-H as follows: To a stirred solution of the above cyano-alcohol (99 mg, 0.27 mmol) in toluene (5 mL) at -78 °C, was added Dibal-H reagent (0.44 mL, 0.93 M in toluene, 0.41 mmol). The mixture was stirred at -78 °C for 30 min, then quenched with methanol (3 mL), extracted with ether (3x15 mL), washed with sodium hydroxide (10%, 5 mL), brine (5 mL) and water (5 mL), dried over Na_2SO_4, and concentrated *in vacuo*. Flash chromatography of the residue (silica gel, 15% ethyl acetate in hexane) gave the corresponding aldehyde (79 mg, 79%). To a portion of this aldehyde (40 mg, 0.11 mol) was added sodium borohydride (16 mg, 0.22 mmol) in methanol and the mixture was stirred at 0 °C for 30 min, then quenched with 10% HCl (2 mL), extracted with ether (3x20 mL), washed with brine (5 mL), dried over Na_2SO_4, and concentrated *in vacuo*. Flash chromatography of the residue (silica gel, 20% ethyl acetate in hexane) gave ether-diol **11** (39 mg, 97%). **11**: a white solid, mp 105-106 °C; IR ($CHCl_3$) 3430, 2967, 1564, 962 cm^{-1}; ^1H NMR δ 4.26 (1H, br m, H-10), 3.93 (1H, dt, *J*=10, 6 Hz, H-2), 3.40 (2H, s, -CH_2OH), 1.92 (1H, dd, *J*=12, 3 Hz, H-3α), 1.89 (1H, dd, *J*=12, 3 Hz, H-5α), 1.78 (1H, m, H-1), 1.74 (2H, m, H-8ß, H-7), 1.62-1.50 (3H, m), 1.34 (1H, m), 1.14 (1H, dd, *J*=13, 4 Hz), 0.98 (3H, s, 4-CH_3), 0.92 (9H, s), 0.89 (3H, d, *J*=7 Hz), 0.84 (3H, d, *J*=7 Hz), 0.09 (3H, s), 0.07 (3H, s); LR-EI-MS *m/z* 369 (M^+), 355, 321, 221, 203, 147.

(2β,4aα,5β,8α,8aα)-5-[(tert-Butyldimethylsilyl)oxy]-1,2,4a,5,6,7,8,8a-octahydro-2-methyl-8-(1-methylethyl)-2-naphthaldehyde 3: To a well stirred solution of butyllithium (4.0 mL, 1.62 M in hexane, 6.5 mmol) in anhydrous THF (20 mL) at -78 °C was slowly added a solution of *N*-benzylidenaminomethylphosphonate (1.58 g, 0.65 mmol) in THF (10 mL), and the red solution was stirred at -78 °C for an additional 1 h. α, ß- Unsaturated ketone **4** in THF (5 mL) was then added dropwise and allowed to warm up slowly to 25 °C for 2 h with stirring. The reaction mixture was recooled to -78 °C and butyllithium (6.68 mL, 1.62 M in hexane, 10.8 mmol) was slowly added. After stirring for an additional 1 h, iodomethane (2.67 g, 18.8 mmol) was added, the cooling bath was removed and the reaction mixture was stirred at room temperature for 2 h. The solution was then added to 1 M HCl (15 mL), and the resulting heterogeneous mixture was stirred vigorously at rt for 2 h. Brine (25 mL) was added, and the aqueous layer was extracted with ether (3x80 mL). The combined organic layers were washed with saturated $NaHCO_3$ (30 mL), dried over Na_2SO_4, and concentrated *in vacuo*. Flash chromatography of the residue (silica gel, 5% ethyl acetate in hexane) gave aldehyde **3** as a colorless oil (948 mg, 87%). **3**: IR (neat) 2989, 2819, 1725,1641 cm^{-1}; ^1H NMR δ 9.50 (1H, s), 6.06 (1H, d, *J*=11 Hz), 5.70 (1H, d, *J*=11 Hz), 3.67 (1H, dt, *J*=11, 4 Hz), 2.45 (1H, m), 1.92-1.70 (2H,

m), 1.47-1.16 (3H, m), 1.09 (3H, s), 0.89 (9H, s), 0.81 (3H, d, *J*=7 Hz), 0.73 (3H, d, *J*=7 Hz), 0.04 (3H, s), 0.03 (3H, s).

(2β,4aα,5β,8α,8aα)-5-[(tert-Butyldimethylsilyl)oxy]-1,2,4a,5,6,7,8,8a-octahydro-2-hydroxymethyl-2-methyl-8-(1-methylethyl)-naphthalene 14: Sodium borohydride (206 mg, 5.42 mmol) was added to a stirred solution of **3** (948 mg, 2.71 mmol) in methanol (10 mL). The mixture was stirred at 0 °C for 30 min, then quenched with 10% HCl (5 mL), extracted with ether (3x40 mL), washed with brine (5 mL) , dried over Na_2SO_4, and concentrated *in vacuo*. Flash chromatography of the residue (silica gel, 20% ethyl acetate in hexane) gave olefin-alcohol **14** as a colorless oil (864 mg, 91%). **14**: IR (neat) 3651, 2980, 1647 912 cm^{-1}; ^1H NMR δ 5.77 (1H, dd, *J*=10, 4 Hz, H-2), 5.50 (1H, dd, *J*=10, 3 Hz, H-3), 3.79 (1H, dt, *J*=7, 3 Hz, H-10), 3.35 (2H, s, $-CH_2OH$), 2.28 (1H, br m, H-1), 2.12 (1H, dd, *J*=13, 8 Hz, H-5α), 1.84 (1H, m), 1.80 (1H, m, H-7), 1.68 (1H, m), 1.59 (1H, m, H-9α), 1.40 (1H, m, H-9ß), 1.21 (1H, m), 1.12 (1H, dd, *J*=13, 3 Hz, H-5β), 1.02 (3H, s), 0.91 (3H, d, *J*=7 Hz), 0.88 (9H, s), 0.79 (3H, d, *J*=7 Hz), 0.03 (3H, s), 0.01 (3H, s); LR-EI-MS *m/z* 352 (M^+), 337, 321, 295, 203, 119; HR-EI-MS, calcd for $C_{21}H_{40}O_2Si$ (M^+) 352.2798, found 352.2772.

(1α,2α,3β,4aα,5α,8β,8aα)-8-[(tert-Butyldimethylsilyl)oxy]decahydro-3-hydroxymethyl-3-methyl-5-(1-methylethyl)-3H,4H-naphthaleno[1,2-b]oxirane 15: To a solution of olefin-alcohol **14** (1.46 g, 4.15 mmol) in dichloromethane was added *m*-CPBA (880 mg, 5.1 mmol) and the mixture was stirred at rt for 5 h, then diluted with ether (100 mL), washed with saturated $NaHCO_3$ (5 mL), brine (5 mL), dried over Na_2SO_4, and concentrated *in vacuo*. Flash chromatography of the residue (silica gel, 10% ethyl acetate in hexane) afforded epoxide **15** as a colorless oil (1.53 g, 100%). **15**: IR (neat) 3470, 2960, 2860, 1578, 1254, 1030, 897 cm^{-1}; ^1H NMR δ 4.01 (1H, br s, H-10), 3.51 (1H, d, *J*=9 Hz, $-CH_2OH$), 3.28 (1H, d, *J*=9 Hz, $-CH_2OH$), 3.14 (1H, br d, *J*=4 Hz), 3.05 (1H, br d, *J*=4 Hz), 2.01 (1H, br t, *J*=3 Hz), 1.88-1.55 (4H, m), 1.43 (1H, m), 1.27 (1H, m), 1.06 (3H, s), 0.90 (9H, s), 0.90 (3H, d, *J*=7 Hz), 0.81 (3H, d, *J*=7 Hz), 0.06 (3H, s), 0.05 (3H, s); LR-FAB-MS *m/z* 369 $(M+H)^+$, 351, 293, 237, 201; HR-FAB-MS, calcd for $C_{21}H_{41}O_3Si$ $(M+H)^+$ 369.2825, found 369.2838.

(1α,3β,4aα,5α,8β,8aα)-8-[(tert-Butyldimethylsilyl)oxy]decahydro-3-hydroxymethyl-3-methyl-5-(1-methylethyl)-1-naphthol 16: A mixture of epoxide **15** (437 mg, 1.2 mmol) and $LiAlH_4$ (226 mg, 6 mmol) in dioxane (24 mL) was stirred at 80-85 °C for 1.5 h. After cooling to rt, the reaction mixture was quenched with ethyl acetate (6 mL) and 1M HCl (5 mL), extracted with ether (3x60 mL), washed with 10% NaOH (5 mL), brine (5 mL), dried over Na_2SO_4, and concentrated *in vacuo*. Flash chromatography of the residue (silica gel, 10% methanol in dichloromethane) afforded triol **16** as a colorless oil (227 mg, 75%) and C-2 position reduced triol and diol (22%). **16**: IR (neat) 3600, 2940, 1387, 1074, 910, 823 cm^{-1}; ^1H NMR δ 4.26 (1H, td *J*=10, 4 Hz, H-2), 3.86 (1H, dt, *J*=10, 4 Hz, H-10), 3.52 (1H, d, *J*=10 Hz, $-CH_2OH$), 3.45 (1H, d, *J*=10 Hz, $-CH_2OH$), 2.10-1.82 (6H, m), 1.73-1.60 (3H, m), 1.34 (1H, tt, *J*=12, 3 Hz, H-7), 1.19 (1H, dd, *J*=13, 11 Hz, H-3α), 1.12 (1H, dd, *J*=13, 6 Hz), 0.98 (3H, s), 0.90 (3H, d, *J*=7 Hz), 0.68 (3H, d, *J*=7 Hz); LR-EI-MS*m/z* 256 (M^+), 238, 201, 189, and 177; HR-EI-MS, calcd for $C_{15}H_{28}O_3$ (M^+) 256.2039, found 256.2043.

(1α,3β,4aα,5α,8β,8aα)-8-[(tert-Butyldimethylsilyl)oxy]decahydro-3-[(tert-butyldimethylsilyl)oxymethyl]-3-methyl-5-(1-methylethyl)-1-naphthol 17: To a stirred mixture of **16** (92 mg, 0.36 mmol), triethylamine (109 mg, 1.08 mmol) and DMAP (2 mg, 0.016 mmol) in dichloromethane (5 mL) at -20 °C, was added TBSOTf (190 mg, 0.72 mmol). The mixture was stirred at -20 °C for 30 min, diluted with ether (40 mL), washed with 5% HCl (2 mL), brine (5 mL) and water (5 mL), dried over Na_2SO_4, and concentrated *in vacuo*. Flash chromatography of the residue (silica gel, 5% ethyl acetate in hexane) afforded **17** as a colorless oil (152 mg, 87%). **17**: IR (neat) 3500, 2950, 2945, 2855, 820 cm^{-1}; ^1H NMR δ 5.23 (1H, s, -OH), 4.20 (1H, td, *J*=11, 4 Hz), 3.86 (1H, dt, *J*=11, 5 Hz, H-10), 3.45 (1H, d, *J*=10 Hz, CH_2OH), 3.31 (1H, d, *J*=10 Hz, CH_2OH), 2.14 (1H, m), 2.00 (1H, d, *J*=14 Hz), 1.90 (1H, dd, *J*=14, 3 Hz), 1.80-1.50 (4H, m), 1.48-1.20 (3H, m), 1.13 (1H, dd, *J*=14, 12 Hz, H-3α), 0.99 (1H, dd, *J*=14, 6 Hz), 0.90 (12H, s), 0.88 (9H, s), 0.86 (3H, d, *J*=7 Hz), 0.65 (3H, d, *J*=7 Hz), 0.11 (3H, s), 0.09 (3H, s), 0.02 (3H, s), 0.01 (3H, s); LR-FAB-MS *m/z* 485 $(M+H)^+$, 467, 221, 203; HR-EI-MS, calcd for $C_{27}H_{57}O_3Si_2$ $(M+H)^+$ 485.3846, found 485.3798.

(3β,4aα,5α,8β,8aα)-8-[(tert-Butyldimethylsilyl)oxy]octahydro-3-[(tert-Butyldimethylsilyl)oxymethyl]-3-methyl-5-(1-methylethyl)-1(2H)-naphthalenone 18: A mixture of **17** (574 mg, 1.19 mmol), PDC (1.32 g, 3.55 mmol), and 4Å molecular sieves (200 mg) in dichloromethane (25 mL) was stirred at rt for 5 h. The resulting mixture was filtered and washed with ether (2x20 mL). The combined washings were concentrated *in vacuo* and the resulting residue purified by flash chromatography (silica gel, 5% ethyl acetate in hexane) to afford bis-TBS ketone **18** as a colorless oil (570 mg, 99%). **18**: IR (neat) 2956, 1713 cm^{-1}; ^1H NMR ($CDCl_3$), δ 4.06 (1H, d, *J*=3 Hz), 3.33 (2H, s), 2.34 (1H, d, *J*=15 Hz), 2.21 (1H, d, *J*=15 Hz), 2.08 (1H, t, *J*=13 Hz), 1.92 (1H, m), 1.70-1.50 (4H, m), 1.43 (1H, m), 1.31 (1H, m), 1.19 (1H, d, *J*=15 Hz), 1.10 (1H, m), 1.02 (1H, dd, *J*=15, 7 Hz), 0.95 (3H, s), 0.91 (3H, d, *J*=7 Hz), 0.90 (9H, s), 0.89 (9H, s), 0.86 (3H, d, *J*=7 Hz), 0.06 (6H, s), 0.02 (6H, s); LR-EI-MS *m/z* 482 (M^+), 467, 21; HR-EI-MS, calcd for $C_{27}H_{54}O_3Si$ (M^+) 482.3640, found 482.3629.

(3β,4aα,5α)-3-[(tert-Butyldimethylsilyl)oxymethyl]-3,4,4a,5,6,7-hexahydro-3-methyl-5-(1-methylethyl)-1(2H)-naphthalenone 19: A solution of **18** (373 mg, 0.77 mmol) and DBU (235 mg, 1.54 mmol) in xylene (15 mL) was refluxed for 5 h. After cooling to rt, the resulting mixture was diluted with ether (50 mL), washed with 5% HCl (1 mL), brine (5 mL) and water (5 mL), dried over Na_2SO_4, and concentrated *in vacuo*. Flash chromatography of the residue (silica gel, 5% ethyl acetate in hexane) afforded α, ß-unsaturated ketone **19** as a colorless oil (256 mg, 95%). **19**: IR (neat), 2970, 1687, 1630, 1380, 817 cm^{-1}; ^1H NMR δ 6.69 (1H, m), 3.30 (1H, d, *J*=9 Hz), 3.27 (1H, d, *J*=9 Hz), 2.38 (1H, br m), 2.34 (1H, d, *J*=17 Hz), 2.17 (1H, dd, *J*= 17, 3 Hz), 2.01 (1H, m), 1.78-1.65 (2H, m), 1.35-1.18 (4H, m), 0.97 (3H, d, *J*=7 Hz), 0.93 (3H, s), 0.89 (9H, s), 0.77 (3H, d, *J*=7 Hz), 0.07 (3H, s), 0.03 (3H, s); LR-EI-MS *m/z* 351 $(M+H)^+$, 335, 293, 223, 159, 145; HR-EI-MS, calcd for $C_{21}H_{39}O_2Si$ $(M+H)^+$ 351.2720, found 351.2692.

(3β,4aα,5α,8α,8aβ)-3-[(tert-Butyldimethylsilyl)oxymethyl]octahydro-3,8-dimethyl-5-(1-methylethyl)-1[2H]-naphthalenone 20: To a stirred suspension of CuI (218 mg, 1.1 mmol) in THF (5.0 mL) at -78 °C was added MeLi (1.52 mL, 1.5 M in ether, 2.3 mmol), then the mixture was allowed to warm until homogenous and was recooled to -78 °C, where BF_3•OEt_2 (162 mg, 1.2 mmol) was added *via* syringe. A solution of α,ß-unsaturated ketone **19** (200 mg, 0.57 mmol) in THF (3 mL) was then added, and the mixture was stirred for 1 h. The resulting mixture was quenched with 5 mL of a 1:9 mixture of conc. NH_4OH and saturated NH_4Cl solution, extracted with ether (3x30 mL), washed with brine (5 mL), dried over Na_2SO_4, and concentrated *in vacuo*. Flash chromatography of the residue (silica gel, 5% ethyl acetate in hexane) afforded TBS ketone **20** as a colorless oil (160 mg, 76%), and deprotected ketone-alcohol **20a** as a colorless oil (22 mg, 15%). **20**: IR (neat) 2956, 2854, 1732, 1470, 1389, and 837 cm^{-1}; ^1H NMR δ 3.29 (1H, d, *J*=10 Hz, $-CH_2OH$), 3.22 (1H, d, *J*=10 Hz, $-CH_2OH$), 2.37 (1H, br m, H-10), 2.32 (1H, d, *J*=14 Hz, H-3ß), 2.01 (1H, m, isopropyl), 1.97 (1H, dd, *J*=14, and 3 Hz, H-3α), 1.92 (1H, br dd, *J*=11, 3 Hz, H-1), 1.86 (1H, qd, *J*=11, 3 Hz, H-6), 1.67 (1H, dt, *J*=14, 2 Hz, H-5α), 1.62 (1H, dq, *J*=14, 4 Hz, H-9α), 1.43 (1H, m, H-9ß), 1.41 (1H, m, H-8ß), 1.31 (1H, t, *J*=12 Hz, H-5ß), 1.26 (1H, m, H-8α), 1.14 (1H, tt, *J*=10, 3 Hz, H-7), 0.95 (3H, d, *J*=7 Hz, 10-Me), 0.93 (3H, d, *J*=7 Hz), 0.89 (9H, s), 0.79 (3H, s, 4-Me), 0.76 (3H, d, *J*=7 Hz), 0.07 (3H, s), 0.03 (3H, s); LR-EI-MS *m/z* 367 $(M+H)^+$, 351, 335, 309, 293, 217; HR-EI-MS, calcd for $C_{22}H_{42}O_2Si$ (M^+) 366.2954, found 366.2927. **20a**: IR (neat) 3406, 2956, 1704, 1578, 1467, 1035, 888 cm^{-1}; ^1H NMR δ 3.37 (1H, d, *J*=10 Hz), 3.34 (1H, d, *J*=10 Hz), 2.37 (1H, m), 2.33 (1H, d, *J*=14 Hz), 2.10-2.00 (1H, m), 2.03 (1H, dd, *J*=14, 3 Hz), 1.94 (1H, dd, *J*=11, 3 Hz), 1.87 (1H, qd, *J*=11, 4 Hz), 1.76 (1H, dt, *J*=13, 2 Hz), 1.66-1.53 (1H, m), 1.52-1.38 (2H, m), 1.32 (1H, t, *J*=11 Hz), 1.16 (1H, tt, *J*=10, 3 Hz), 0.96 (3H, d, *J*=7 Hz), 0.92 (3H, d, *J*=7 Hz), 0.84 (3H, s), 0.77 (3H, d, *J*=7 Hz); LR-EI-MS *m/z* 252 (M^+), 216.

Reprotection of (3β,4aα,5α,8α,8aβ)-Octahydro-3-hydroxymethyl-3,8-dimethyl-5-(1-methylethyl)-1(2H)-naphthalenone 20a: To a stirred mixture of ketone-alcohol **20a** (22 mg, 0.089 mmol), triethylamine (18 mg, 0.18 mmol) and DMAP (2 mg, 0.02 mmol) in dichloromethane (3 mL) at -20 °C, was added TBSOTf (28 mg, 0.09 mmol). The mixture was stirred at -20 °C for 30 min, then extracted with ether (3x10 mL), washed with 5% HCl (2 mL), brine (5 mL), dried over Na_2SO_4, and concentrated *in vacuo*. Flash chromatography of the residue (silica gel, 5% ethyl acetate in hexane) yielded **20** (32 mg, 98%).

(1α,3β,4aα,5α,8α)-3-[(tert-Butyldimethylsilyl)oxymethyl]decahydro-3,8-dimethyl-5-(1-methylethyl)-1-naphthol 21: Sodium borohydride (33 mg, 0.9 mmol) was added to a stirred solution

of **20** (160 mg, 0.44 mmol) in methanol (10 mL) at rt, and the mixture was stirred for 1 h. An additional portion of sodium borohydride (33 mg, 0.9 mmol) was added and stirred for further 30 min, quenched with 5% HCl (5 mL), extracted with ether (90 mL), washed with brine (5 mL), dried over Na_2SO_4, and concentrated *in vacuo*. Flash chromatography of the residue (silica gel, 5% ethyl acetate in hexane) gave TBS alcohol **21** as colorless oil (138 mg, 86%). **21**: IR (neat) 3640, 2980, 2890, 2860, 1470, 837 cm^{-1}; ^1H NMR δ 4.07 (1H, dt, *J*=7, 2 Hz), 3.14 (1H, d, *J*=10 Hz), 3.11 (1H, d, *J*=10 Hz), 2.06-1.89 (3H, m), 1.81 (1H, qd, *J*=11, 4 Hz, H-6), 1.70-1.20 (7H, m), 1.15 (1H, tdd, *J*=14, 4, 2 Hz, H-7), 1.06 (3H, s), 0.95 (3H, d, *J*=7 Hz), 0.90 (9H, s), 0.78 (3H, d, *J*=7 Hz), 0.02 (6H, s); LR-EI-MS *m/z* 367 $(M-H)^+$, 351, 335, 309, 293, 219, 163; HR-EI-MS, calcd for $C_{22}H_{44}O_2Si$ (M^+) 368.3110, found 368.3109.

(1α,4α,4aα,6β)-6-[(tert-Butyldimethylsilyl)oxymethyl]-1,2,3,4,4a,5,6,7-octahydro-1,6-dimethyl-4-(1-methylethyl)-naphthalene 22: To a stirred solution of **21** (138 mg, 0.38 mmol) in pyridine (5.0 mL) was added thionyl chloride (223 mg, 1.9 mmol) at 0 °C, and the reaction mixture was stirred for 1 h, then diluted with ether (100 mL), washed with 10% HCl (5 mL), brine (5 mL), dried over Na_2SO_4, and concentrated *in vacuo*. Flash chromatography of the residue (silica gel, 3% ethyl acetate in hexane) gave olefin-ether **22** as a colorless oil (131 mg, 100%). **22**: IR (neat) 2956, 2932, 2874, 1608, 1578, and 987 cm^{-1}; ^1H NMR δ 5.35 (1H, d, *J*=6 Hz), 3.25 (2H, s), 2.42 (1H, m), 2.12-2.02 (1H, m), 1.98-1.87 (2H, m), 1.62-1.48 (5H, m), 1.42 (1H, m), 1.35 (1H, dd, *J*=12, 4 Hz), 1.05 (3H, d, *J*=7 Hz), 0.90 (9H, s), 0.89 (3H, d, *J*=7 Hz), 0.78 (3H, d, *J*=7 Hz), 0.02 (6H, s); LR-EI-MS *m/z* 350 (M^+), 335, 309, 218, 175; HR-EI-MS, calcd for $C_{22}H_{44}OSi$ (M^+) 350.3005, found 350.2987.

(1α,4α,4aα,6β)-1,2,3,4,4a,5,6,7-Octahydro-6-hydroxymethyl-1,6-dimethyl-4-(1-methylethyl)-naphthalene 23: A mixture of **22** (19.8 mg, 0.057 mmol) and TBAF (0.17 mL, 1.0 M in THF, 0.17 mmol) in THF (2.0 mL) was stirred at 40 °C overnight. After cooling to rt, the reaction mixture was diluted with ether (100 mL), washed with 5% HCl (1 mL), brine (5 mL), dried over Na_2SO_4, and concentrated *in vacuo*. Flash chromatography of the residue (silica gel, 10% ethyl acetate in hexane) gave olefin-alcohol **23** (13.8 mg, 100%). **23**: a colorless oil; IR (neat) 3400, 2960, 2930, 2880, 1665, 1578, 1470, 1374 cm^{-1}; ^1H NMR δ 5.35 (1H, d, *J*=5 Hz), 3.34 (2H, s), 2.44 (1H, br m), 2.09 (1H, br m), 1.96 (1H, m), 1.93 (1H, m), 1.70-1.52 (4H, m), 1.47-1.41 (2H, m), 1.37 (1H, dd, *J*=12, 4 Hz), 1.05 (3H, d, *J*=7 Hz), 0.89 (3H, d, *J*=7 Hz), 0.85 (3H, s), 0.78 (3H, d, *J*=7 Hz); LR-EI-MS *m/z* 236 (M^+), 205, 193, 175, 135; HR-EI-MS, calcd for $C_{16}H_{28}O$ (M^+) 236.2140, found 236.2114.

(2β,5α,8α,8aα)-1,2,3,5,6,7,8,8a-Octahydro-2,5-dimethyl-8-(1-methylethyl)-2-naphthoic acid 2: To a stirred solution of the olefin-alcohol **23** in acetone (2.0 mL) at 0 °C was added Jones' reagent (150 μL), and the mixture was stirred at 0 °C for 50 min, then quenched with *i*-PrOH (0.5 mL), diluted with water (10 mL), extracted with ether (3x10 mL), washed with brine (5 mL), dried over Na_2SO_4, and concentrated *in vacuo*. Flash chromatography of the residue (silica gel, 10% ethyl acetate in hexane) gave olefin-acid **2** as a white solid (13 mg, 94%). **2**: mp 120-121 °C; IR ($CHCl_3$) 3400 (br), 2926, 2854, 1734, 1581, 915 cm^{-1}; ^1H NMR δ 5.38 (1H, t, *J*=5 Hz), 2.44 (1H, br m, H-10), 2.42 (1H, br d, *J*=17 Hz, H-3ß), 2.10 (1H, m, H-6), 1.97-1.86 (3H, m, H-5α , H-11, H-3α), 1.64-1.31 (5H, m, H-9α, H-5ß, H-9ß, H-8α, H-8β), 1.17 (3H, s, 4-Me), 1.01 (1H, tt, *J*=11, 2 Hz, H-7), 0.89 (3H, d, *J*=7 Hz), 0.79 (3H, d, *J*=7 Hz); LR-EI-MS *m/z* 250 (M^+), 207, 161; HR-EI-MS, calcd for $C_{16}H_{26}O_2$ (M^+) 250.1933, found 250.1928.

(1α,4α,4aα,6β)-1,2,3,4,4a,5,6,7-Octahydro-6-isocyanato-1,6-dimethyl-4-(1-methylethyl)-naphthalene 25: To a suspension of oil-free KH (19.6 mg, 0.49 mmol) in THF (3.0 mL) at 0 °C was added **2** (12.3 mg, 0.05 mmol). After stirring for 5 min, DPPA (135 mg, 0.5 mmol) in THF (1 mL) was added, and the mixture was stirred at 0 °C for 2.5 h, then diluted with ether (20 mL), washed with brine (3 mL) and water (3 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The resulting residue was refluxed in xylene (5.0 mL) for 5 h, then cooled to room temperature, diluted with ether (20 mL), washed with brine (3 mL), dried over Na_2SO_4, and concentrated *in vacuo*. Flash chromatography of the residue (silica gel, 5% ethyl acetate in hexane) gave olefin-isocyanate **25** as a colorless oil (12 mg, 98%). **25**: IR (neat) 2960, 2932, 2868, 2252, 1668, 1492, 1290, 822 cm^{-1}; ^1H NMR δ 5.34 (1H, d, *J*=6Hz, H-2), 2.43 (1H, br quintet, *J*=6 Hz, H-11), 2.37 (1H, d, *J*=16 Hz, H-3ß), 2.10 (1H, br m, H-6), 1.95 (1H, heptet d, *J*=7, 3 Hz, isopropyl), 1.94-1.81 (2H, m, H-8ß, and H-3α), 1.58 (1H, m, H-5α), 1.53 (1H, dt, *J*=13, and 4 Hz, H-9α), 1.44 (1H, tt, *J*=13, and 4 Hz, H-9ß), 1.32 (1H, qd, *J*=13, 4 Hz, H-8α), 1.30 (1H, dd, *J*=14, 11 Hz, H-5ß), 1.14 (3H, s, 4-Me),

1.04 (3H, d, J=7 Hz), 1.01 (1H, tt, J=13, 4 Hz, H-7), 0.79 (3H, d, J=7 Hz); LR-EI-MS m/z 247 (M^+), 204, 161, 121, 105; HR-EI-MS, calcd for $C_{16}H_{25}ON$ (M^+) 247.1936, found 247.1934.

(1α,4α,4aα,6β)-1,2,3,4,4a,5,6,7-Octahydro-6-isocyano-1,6-dimethyl-4-(1-methylethyl)-naphthalene 27: Lithium triethylborohydride (73 μL, 1.0 M in THF, 0.07 mmol) was added to a stirred solution of olefin-isocyanate **25** (12 mg, 0.05 mmol) in THF (2.0 mL) at -78 °C, and the mixture was stirred at -78 °C for 1 h, then saturated aqueous $NaHCO_3$ (1.0 mL) was added. The mixture was warmed to rt, diluted with ether (20 mL), washed with brine (2x3 mL), dried over Na_2SO_4, and concentrated *in vacuo*. Flash chromatography of the residue (silica gel, 10% methanol in dichloromethane) gave the corresponding olefin-formamide (12 mg, 96%), which was treated with *p*-toluenesulfonyl chloride (12 mg, 0.06 mmol) in pyridine at rt for 15 h, and then cooled to 0 °C. Ice-water (1 mL) was added and the mixture was stirred at 0 °C for 30 min, diluted with hexane (15 mL), and washed with 5% HCl (2x3 mL), brine (3 mL), dried over Na_2SO_4, and concentrated *in vacuo*. Flash chromatography of the residue (silica gel, 1% ethyl acetate in hexane) gave olefin-isocyanide **27** as colorless oil (4.1 mg, 87%). **27**: IR (neat) 2956, 2866, 2386, 1581, 1380, 1070, 819 cm^{-1}; ^{1}1.93 (1H, heptet d, J=7, 3 Hz, isopropyl), 1.66-1.51 (2H, m), 1.45 (1H, m), 1.34-1.20 (2H, m), 1.25 (3H, s), 1.08 (1H, tt, J=11, 3 Hz, H-7), 1.01 (3H, d, J=7 Hz), 0.92 (3H, d, J=7 Hz), 0.81 (3H, d, J=7 Hz). LR-EI-MS m/z 231 (M^+), 204, 188, 161, 121; HR-EI-MS, calcd for $C_{16}H_{25}N$ (M^+), 231.1987, found 231.2014.

Halipanicine 1: A mixture of olefin-isocyanide **27** (2.5 mg, 0.011 mmol) and sulfur powder (0.7 mg, 0.022 mmol) in xylene (0.25 mL) was heated at 120-125 °C for 4 h, then cooled to rt, diluted with hexane (15 mL), washed with brine (3 mL), dried over Na_2SO_4, and concentrated *in vacuo*. Flash chromatography of the residue (silica gel, hexane) gave halipanicine **1** (1.8 mg, 63%). **1**: IR (neat) 2956, 2926, 2866, 2068 , 1578, 1470, 1377, and 1147 cm^{-1}; ^{1}H NMR δ 5.28 (1H, dt, J=6, 2 Hz, H-2), 2.45 (1H, br quintet, J=7 Hz, H-10), 2.41 (1H, dt, J=16, 2 Hz, H-3ß), 2.12 (1H, ddt, J=16, 6, and 2 Hz, H-3a), 2.10 (1H, m, H-6), 2.03 (1H, ddd, J=13, 6, 2 Hz, H-5α), 1.92 (1H, heptet d, J=7, 3 Hz, isopropyl), 1.64-1.51 (3H, m, H-5ß, H-9α, and H-9ß), 1.45 (1H, dq, J=16, 3 Hz, H-8ß), 1.35 (3H, s), 1.33 (1H, qd, J=13, 4 Hz, H-8), 1.09 (1H, tt, J=13, 3 Hz), 1.01 (3H, d, J=7 Hz), 0.91 (3H, d, J=7 Hz), 0.79 (3H, d, J=7 Hz); LR-EI-MS m/z 263 (M^+), 204, 161, 121; HR-EI-MS, calcd for $C_{16}H_{25}NS$ (M^+) 263.1708, found 263.1726 .H NMR δ 5.28 (1H, d, J=6 Hz), 2.52-2.39 (2H, m, H-10, and H-3β), 2.18 (1H, m), 2.13-1.97 (2H, m),

Acknowledgment: We thank the financial support for Mr. Bin Ye from Fujisawa and Naito Fundation.

References:

1. a) Edenborough, M. S.; Herber, R. B. *Nat. Prod. Rep.*, **1988**, *5*, 229-245. b) Pintao, A. M.; Pais, M. S.; Coley, H.; Kelland, L. R.; Judson, I. R. *Planta Med.*, **1995**, *61*, 233-236. c) Jiao, D.; Ho, C. T.; Foils, P.; Chung, F. L. *Cancer Epidemil Biomarkers Prev.*, **1994**, 3, 487-492. d) He, H. Y., Faulkner, D. J.; Shumsky, J. S.; Hong, K.; Clardy, J. *J. Org. Chem.*, **1989**, *54*, 2511-2514.
2. Chang, A. C.; Takemori, A. E.; Ojala, W. H.; Gleason, W. B.; Portoghese, P. S. *J. Med. Chem.*, **1994**, *37*, 4490-4498.
3. a) Kumar, Y.; Green, R.; Wise, D. S.; Wotring, L. L.; Townsend L. B. *J. Med. Chem.*, **1993**, *37*, 3843-3840 and 3849-3852. b) Posner, G. H.; Cho, C. G.; Green, J. V.; Zhang, Y.; Talalay P. *J. Med. Chem.*, **1994**, *37*, 170-176.
4. Nakamura, H.; Deng, S. Z.; Takamatsu, M.; Kobayashi, J.; Ohizumi, Y.; Hirata, Y. *Agric. Biol. Chem.*, **1991**, *55*, 581-583.
5. Nakamura, H.; Ye, B.; Murai, A. *Tetrahedron Lett.*, **1992**, *33*, 8113-8116.
6. Plfister, J. R.; Wymann, W. E. *Synthesis*, **1983**, 38-40.
7. Danishefsky, S.; Kitahara T. *J. Am. Chem. Soc.*, **1974**, *96*, 7807-7808.
8. (±)-Cryptone was prepared from 4-isopropylphenol, Soffer, M. D.; Jevnik, M. A. *J. Am. Chem. Soc.*, **1955**, *77*, 1003-1006.
9. Burk, L. A.; Soffer, M. D. *Tetrahedron Lett.*, **1971**, 4367-4370.
10. Sarett, L. H.; Lukes, R. M.; Poos, G. I.; Robinson, J. M.; Beyler, R. E.; Vandegrift, J. M.; Arth, G. E. *J. Chem. Soc.*, **1937**, 2255.
11. Martin, S. F.; Puckette, T. A.; Philips, G. W.; Colapret, J. A. *J. Am. Chem. Soc.*, **1980**, *102*, 5866-5872.
12. Utimoto, K.; Obayashi, M.; Shishiyama, Y.; Inoue, M.; Nozaki, H. *Tetrahedron Lett.*, **1980**, *21*, 3389-3392.
13. Yamauchi, K.; Kinoshita, M.; Imoto, M. *Bull. Chem. Soc. Jpn.*, **1972**, *45*, 2531-2534.
14. Boeckman, Jr., R. K.; Silver, S. M. *J. Org. Chem.*, **1975**, *40*, 1755-1759.
15. Lipshutz, B. H.; Ellsworth, E. L.; Siahaan, T. J., *J. Am. Chem. Soc.*, **1989**, *111*, 1351-1358.
16. Ninomiya, K., Shioiri, T., and Yamada, S. *Tetrahedron.*, **1974**, *30*, 2151-2157.
17. Chenera, B.; Chung, C. P.; Hart, D. J.; Lai, C. S. *J. Org. Chem.*, **1992**, *57*, 2018-2029.
18. Boyer, J. H.; Ramakrishnan, V. T. *J. Org. Chem.*, **1972**, *37*, 1360-1364.

(*Received in Japan* 9 *February* 1996; *accepted* 13 *March* 1996)